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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,045	01/03/2002	Jon Elliot Adler	P 280681 2001-019	3276

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,045	ADLER ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *235-267* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *235 and 237-267* is/are rejected.

7)☐ Claim(s) *236* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O

DETAILED ACTION

Status of Application: Claims and Amendments

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Applicant is notified that the amendments put forth on 4/29/05, have been entered in full.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

Maintained Rejections:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 235 and 237-267 are rejected under 35 U.S.C. 112, first paragraph, as set forth previously regarding claims 1, 4-11, 14-41, 44-51, 56-119, 201-208, 211-222 and for the additional reason set forth below, because the specification, while being enabling for isolated naturally occurring polynucleotides that hybridize to a polynucleotide of SEQ

ID NO: 20 under the stringent conditions set forth in lines 17 and 18 of page 16 of the specification and encode a polypeptide that bind sucrose in conjunction with a T1R3 polypeptide, does not reasonably provide enablement for artificially constructed polynucleotides that encode variants of the polypeptide of SEQ ID NO: 21, and additionally regarding new claims 254, 255, 266 and 267, the specification does not provide enablement for G-proteins other than Gα15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 21, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 21 Applicant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 21, but which still retain a desired property of the polypeptide of SEQ ID NO: 21.

The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Applicant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 21 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 21 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 21 then the specification has failed to teach one of

skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 21.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.).

The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 21 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The problem of producing active variants appears especially difficult in the art of T1R receptors, to which the instant polypeptide is asserted to belong. The instant specification appears to simply suggest to the artisan that art-recognized procedures for screening GPCRs (e.g. pages 32-33, 40 and the example at page 91) are sufficient to identify functional variants of SEQ ID NO: 21. However, Hoon *et al., Cell* 96(541-551)1999, report that AWe have attempted to determine the ligand/tastant specificity of TR1 and TR2 using a variety of strategies but have been hampered by the difficulty of functionally expressing these molecules in heterologous systems≅ see col 1 of page 547. The art regarding T1R receptors, as exemplified by Hoon et al., recognizes the complexity, unpredictability, and non-routine nature of the work involved in trying to

assay functional T1R receptors. The instant specification has provided only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such variants.

Therefore, due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the difficulties encountered in screening T1Rs, exemplified by Hoon et al., and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Additionally, as set forth above regarding 254, 255, 266 and 267, the specification does not provide enablement for G-proteins other than Gα15. The specification simply speculates that the T1R polypeptides would bind to gustducin or the rod specific tranducin, but there is no evidence that it would nor teachings as to how to make modifications so that it would. The specification has simply presented the results using the promiscuous G-protein Gα15, and invited the artisan to try to find others that could.

Thus, the claims are, in essence, single means claims. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope

of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). Further, if the claimed constructs did not respond to sweet taste stimuli, then the specification has failed to use such.

Applicant argues that the specification provides a multitude of assay formats in which the variant polypeptides can be tested. This argument has been fully considered but not deemed persuasive. The issue is that specification has not provided sufficient guidance as to which variants to make such that one would have a reasonable expectation of success in finding such without undue experimentation.

Applicant argues that polypeptides having at least 90% sequence identity or that hybridize are enabled because they are sufficiently similar to the exemplified T1R2 and that this is a reasonable genus consistent with PTO guidelines. This argument has been fully considered but not deemed persuasive. Polypeptides having at least 90% sequence identity would have over 80 amino acid substitutions relative to what has been disclosed, and no particular teaching has been made to show which of the practically limitless combinations of 80 differences could be expected to be useful. Hybridization would matter little to the polypeptide sequence of artificially constructed variants.

Applicant challenges the relevance to the Hoon article, asserting that the specification provides specific information, e.g. ligand binding partner. This argument has been fully considered but not deemed persuasive. Hoon is being relied upon to

demonstrate that the art recognizes the complexity, unpredictability, and non-routine nature of the work involved in trying to assay functional T1R receptors.

Claims 235 and 237-267 are rejected under 35 U.S.C. 112, first paragraph, as set forth previously regarding claims 1, 4, 5, 7-11, 14, 15, 17-41, 44, 45, 47-53, 56, 57, 59-119, 201, 202, 204-208, 211-222, and for the additional reason regarding claims 254, 255, 266 and 267 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a naturally occurring polynucleotide of SEQ ID NO: 20 encoding a polypeptide of SEQ ID NO: 21, yet the claims encompass polynucleotides not described in the specification, e.g., artificially mutated sequences, sequences that have a recited degree of identity or that merely hybridize to SEQ ID NO: 20. These claimed genera do not meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist or could be made to exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by

nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses no artificially mutated sequences that have any function. Further, even if the disclose sequence were definitive of a genus with a specified function, the instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify/obtain the polynucleotides encompassed, thus the artisan would not consider Applicant to be in possession of the breadth that is claimed.

With the exception of the polynucleotide of SEQ ID NO: 20, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants. Therefore, only the polynucleotide of SEQ ID NO: 20, other polynucleotides that encode a polypeptide of SEQ ID NO: 21, and polynucleotides consisting of fragments thereof, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Additionally, as set forth above regarding 254, 255, 266 and 267, one skilled in the art would not expect that Applicant was in possession of the claimed constructs, other than those involving Gα15, that would respond to sweet taste stimuli. The specification simply speculates that the T1R polypeptides would bind to gustducin or the rod specific tranducin, but there is no evidence that it would nor teachings as to how to make modifications so that it would, thus the Artisan would not expect Applicant to be in possession of such.

Applicant's arguments as to the basis of the enablement rejection have been addressed above. Furthermore, Applicant asserts that a structure/function relationship

has been established in the instant specification which obviates Eli Lilly as the basis of the rejection. This argument has been fully considered but not deemed persuasive. One skilled in the art appreciates that percent identity or hybridization conditions provide no specific information regarding structure, these are simply cumulative parameters and describe no particular structure. Thus there is no nexus between structure and function in the claims. The skilled artisan appreciates that simply writing down or verbalizing that a non-described protein should have a specific functional property in no way puts one in possession of such a protein.

Conclusion

Please note the new central fax number for official correspondence below:

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX months.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

July 7, 2005

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600